

English Translation of RU 2065307

Tools for treatment of primary liver cancer AND METHOD TREATMENT OF PRIMARY LIVER CANCER

Field of technology

The invention relates to medicine, more accurately, 5 Oncology, namely for the treatment of primary cancer liver and a method for treating primary liver cancer.

PRIOR ART

Primary liver cancer is one of the most malignant tumors of man. Treatment of patients is 1 On a difficult task. Chance of cure makes the operation made in the early stages of disease, but more often in neoplastic process are involved both lobes of the liver. In addition, accompanying cirrhosis, thrombosis, and massive infiltration of the portal vein are considered as 15 contraindications to surgery, potentially resectable May be up to 30% of patients. Postoperative oslazhneniya heavy, and relapse is more Human silt than the exception. Therefore, the overwhelming number of patients with primary liver cancer shows a conservative 20 treatment. Primary liver cancer is among the resistant to chemotherapy of malignant forms of neoplasms.

The effectiveness of systemic chemotherapy Fluorouracil is extremely low, a slight improvement results achieved by using doxorubicin. 25 Interest in regional chemotherapy continues unabated. The introduction of cytotoxic drugs into the hepatic artery creates a high tumor drug concentration and theoretically should lead to an increase in therapeutic efficacy with a decrease in overall adverse toxic reactions. More likely to 30 regional intrahepatic chemotherapy used doxorubicin by 60-75 mg / m once in 2-6 weeks or of 7-30 mg / m for 72 hours continuously. The maximum life expectancy of patients treated with effect of 20 months., combination chemotherapy 35 doxorubicin and mitomycin C did not improve results treatment

There is a method of treatment with drugs daunorubicin-arachidonic acid and alpha-fetoprotein man. A method of producing these drugs is described in

Journal of Cancer Res., 43, 2668-2672 (1983). *ibid* reported that the combined use of drugs 5 daunorubicin-arachidonic acid and alpha-fetoprotein man leads to cytostatic sinergicheskoiu

Effect in in vitro experiments, when exposed to neoplastic human cell lines that have receptor for alpha-fetoprotein, and in experiments in 10 vivo on animals with entwined human tumors. In 1983, Dr. Kohn was invited to use for targeted delivery of anticancer drugs in some types of tumor tissues hydrophobic compound Lipiodol ultrafluid (Konno T. et al., Eur. J. Cancer Clin. 15 Oncol., 1983, 19, 1053-1065). Initially, this connection was synthesized as a dye for X-rays (Maeda H. et al., Eur. J. Cancer Clin. Oncol., 1983, 9, 543-547) • Lipiodol ultrafluid a poppy-seed oil with 2 O substituted ethyl ether, the ether of glycerol. Viscosity compound at 15 0 to 70 senior, density at 15 0 with -1.28. 1d.

Lipiodol ultrafluid contains 0.38 g of iodine. At intra-arterial injection Lipiodol ultrafluid disperses into small fat droplets. Because of 25 morphological differences between the capillaries of the tumor and normal tissues of the droplets remain in the first and quickly removed from the second (Konno T., Cancer, 1990, 66, 1897-1903). For example, in the tissues of primary liver cancer Lipiodol ultrafluid can be up to 3 months, 3 The metastatic liver cancer, lung cancer and some tumors of the urinary system and sex for several weeks. Of normal tissues as shown in Lipiodol ultrafluid average of 24 hours. This property of Dr. Cohn used for targeted delivery of anticancer drugs in 35 tissues of primary liver cancer. Antitumor drug previously dissolved in Lipiodol and ultrafluid then intravenously administered to a patient. In tumor tissue drug penetrated into rastvorenny fat bubbles Lipiodol ultrafluid, of which place its slow diffusion into the blood. So way Lipiodol ultrafluid serves as a 5 reservoir of anti-cancer drug that can maintain a relatively high concentration of the latter long time. As further research method allows to increase the Kono

efficacy of chemotherapy effects in
10 treatment of primary liver cancer is 2.5-3 times higher than
with the results seen with
anticancer drug in free form. as
anticancer drugs on Dr. Cohn used the
doxorubicin, mitomycin C, 5MANC5, aklarubitsin (Kopp, T.,
1S et al., Eur.J.Cancer, 1992, 28, 403-408).

Some ONKO fetalnye belkhi I in particular protein
serum alpha-fetoprotein, have a unique
property to selectively penetrate sootvetstviu with
mechanism of receptor endocytosis in some types of
20 tumor, but not normal cells (Uriel J. Et al.,
Int.J.Cancer., 1987,40, 314-318; Laborda J., Tumor Biol.,
1984, 5, 41-51). In addition to this extremely important property
AFP bind certain steroid
hormones and Pauline saturated fatty acids (Deutsch N. F.,
25 Adv.Cancer Res., 1991, 56, 253-312). Dr. Deutsch
was first formulated and then experimentally
confirmed the hypothesis about the possibility of directional
transport of anticancer drugs in some types of
tumor cells, using as
3 The transport protein alpha-fetoprotein (Deu tsh N. F.,
Adv.Cancer Res., 1991, 56, 253-312). Content of proposition
Dr. Deutsch method is as follows.
Chemically synthesized covalent complex
daunorubicin-arachidonic acid. Due to a member of the
35 composition of this complex of arachidonic acid was
able to effectively communicate with alpha-fetoprotein and
such as selectively penetrate into some of the tumor,
but not normal cells. The most effective capture
ternary complex of doxorubicin-arachidonic acid
alpha-fetoprotein place cells of hepatocellular
carcinomas (Abelev GI, Tumor. Biol., 1989,10, 63-74).
after
lost
penetration
cytostatic
tumor cell
activity in
reduced overall toxicity.
antibiotic is not
significant
priienenie doxorubicin suspezii with Lipiodol
ultrafluid with intra-arterial injection into the hepatic

10 artery leads to a significant increase (2-3 times compared with obychnyii treatments) the effectiveness of chemotherapy in the treatment of primary liver cancer.

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in
a
liver,
Disclosure of invention
The present invention
the remedy for the treatment of
which would provide
laid task
primary cancer
fast high
antitumor antibiotic concentration in the tumor.
The problem is solved in that means for
growth inhibition
liver containing
As is
tumor
acting
used
primary cancer cells
substance and a carrier in
Lipiodol ultrafluid,
according to the invention, the active substance
used doxorubicin-estrone, and the support of additional
25 contains the lyophilized preparation of alpha-fetoprotein
man.

Although the use of Lipiodol ultrafluida known
for delivery to the tumor tissues of the active substance
proposed combination deksorubitsin-estrone and Lipiodol
30 ultrafluida with the addition of lyophilized preparation
AFP provides not only a man
targeted delivery of doxorubicin in tumor-estrone,
but not normal cells, but also provide high
concentration of antitumor antibiotic in opuh.olevyh
35 tissues, which can significantly improve
effectiveness of treatment for primary liver cancer.
Doxorubicin-estrone can be obtained as described in.

RU, A, N 2026687.

The complex of doxorubicin-estrone is a dark-red crystalline powder formula C₄₉H₄₇O₁₅N molecular weight of 895.96 and the following chemical structure: OH

N.3SH OH ·

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About

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with OH

'OH

H "c ~

but NH O

r 11

o = c ~ c-

- The most expedient to use the following the ratio of active ingredient and the carrier with the addition of: solution of doxorubicin-estrone in 96% ethanol in amount of 20-60 mg 10-15 ml Lipiodol and ultrafluida 20 2-10 mg protein of human alpha-mI saline at 12-15, It is helpful to use a solution doksorubitsinestrona when heated to 70-76 0 C ethanol.

According to the invention for the treatment of primary liver cancer, may be a separate set of 25 tightly packed products, and include sterile doxorubicin-estrone in the amount of 20-60 mg, Lipiodol ultrafluid of 10-15 mg aLfafetoprotein in the amount of 1-10 mg.

We have developed a method of treating spetsialno primary 3 The liver cancer, which includes preparation of the solution active ingredient in Lipiodol ultrafluide and introduction this solution into the hepatic artery, with a active substance use 20-60 ml doksorubitsinestron And it was dissolved in 96% ethanol, heated 35 to 70-76 0 C was added n ~ piodol ultrafluida in the number of 10-15 ml, for 10-30 minutes prior to the introduction of this solution injected into the hepatic artery in alpha-fetoprotein number of 2-10 mg in 12-15 yI of saline solution. Such a method can significantly reduce the side-toxic effects, increase the effectiveness of chemotherapy impact and reduce the dose of anticancer 5 doksorubitsin substance-estrone compared with the applicable at present doses of doxorubicin.

Luchshenie EMBODIMENTS

The patient is prepared for the procedure as an ordinary angiographic study. After percutaneous Catete-10 the polarization of the aorta distal end of the Seldinger catheter installed in the hepatic artery (common or proper hepatic), performed with angiography subsequent analysis of the arterial and venous phases. Under X-ray television control with the help of X-ray 15 contrast agent (verografin, triomtrast) should be see places without shunt in the other, except hepatic system, vascular pools. Freeze-dried sterile preparation of alpha-fetoprotein is introduced intravenously in an amount of 2-10 mg in 12-15 ml 20 saline solution. After 20 minutes, provided lack of immediate adverse toxic effects (Allergic reactions, chest pain, fall blood pressure, tachycardia, tachyarrhythmia) sterile set of Doxorubicin-estrone in the number of 20 - 25 60 mg dissolved in 0,5-1.5 ml of 96% ethanol at heated to 70-7B Hos. The resulting solution was transferred to a 10 - 15 sludge pre-warmed Lipiodol ultrafluida. The resulting slurry is cooled to 32-37 0 C and injected under rentgenotelevideniya control into the hepatic artery. 30 After 3-4 weeks to repeat the administration of drugs alpha-fetoprotein and a range of doxorubicin-estrone on described above.

Total proposed method were treated with 10 patients aged 21 to 65 years old male and female 35 floor. Conditions of pre-selecting patients were as follows: absence of jaundice and ascites, inoperable, no severe concomitant diseases. Assessment of toxicity and effectiveness was conducted by kriteriyam_VOZ. have been studied parahetry following after treatment: duration sequence of remission at the time of treatment to Chala progression in the evaluation of treatment .. stabilization 5 zatsiya, "" minimal, "" partial, "" full effect "and tahzhe life expectancy of patients who were calculated from the start of treatment. In the treatment of patients assigned to the following survey: graiia coagulation, ECG, clinical blood and urine tests, laparoscopy, 10 15 oprelelenie levels of AFP, angiography, computed tomography, ultrasound tomography.

Key findings are presented in
Table 1.

Table 1.

duration

life (months)

20 Control

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Patients polychaemie alpha-fetoprotein and

30 doxorubicin-estrone

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Note: The control patients were, patients with primary liver cancer who underwent conventional 45 course chemotherapy of doxorubicin (60-75 mg / square meters. once in 2-6 weeks or 7-30 mg / m². for 72 hours continuously).

Example 1.

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Excerpt from the case 126/98.

Patient BG : Primary liver cancer.

PCGIRU9S/00030

5 conducted a chemotherapy course is an intra vvedenie alpha-fetoprotein in amount of 4 mg of the drug doxorubicin-estrone in 50 mg with repeated injections after 3 weeks. As a result, the level of alpha-fetoprotein levels decreased 10 to 56 mg / ml (a measure of pre-treatment) to 10 ng / ml after 15 months after treatment. The result was a treat significant improvement of biochemical exponents of blood reduction in tumor size was achieved long bolezni.kv remission.

once in 2-6 weeks or 7-30 mg / m². for

Conclusion: The proposed course of chemotherapy contributes to

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blaropriyatnomu course of the disease. continue treatment under the proposed scheme in case of relapse disease. The patient was observed for 17 months. The final ~ d diagnosis: Long-term remission of the disease, metastases otsuststvuyut Survey) •

Example 2.

(According to

Excerpt from the case 123/57.

Patient LD : Primary liver cancer.

tomographic

The above course is a chemotherapeutic an intra vvedenie alpha-fetoprotein in amount of 6 mg and the drug doxorubicin-estrone in the 60-mg injections with repeated after 4 weeks.

As a result, the level of alpha-fetoprotein levels decreased 30 102 mcg / ml (a measure of pre-treatment) to 8 ng / ml after 16 months after treatment. The result was a treat significant improvement of biochemical exponents of blood disappearance disease.
achieved prolonged remission

35 Conclusion: The proposed course of chemotherapy contributes to favorable course of the disease. Continue treatment under the proposed scheme in case of relapse disease. The patient was observed 20 months. final diagnosis: Long-term remission of the disease, metastases otsuststvyut, the tumor is not detected (according to tomographic examination).
Thus, the proposed method can significantly improve ways to treat cancer diseases.

For the treatment of primary liver cancer may be a set that includes: sterile
10 lyophilized preparation of human alpha-fetoprotein in number of 1-10 mg in bottles with a capacity of 10 ml
sterile drug doxorubicin-estrone in the number of 20 - 60 mg vials with a capacity of 15 ml, sterile
saline 15 ml in an ampoule, 96%
15 ethanol 5 ml in an ampoule, sterile Lipidol
ulotrafluid 20 ml in two 10 ml ampoules.
Set is used as described above, ie
pre-exercise hepatic catheterization
artery. Rengenotelevizionnym under control with the help
20-RENGO contrast medium in the absence of sure
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shunt in the other, except for hepatic system;
vascular pools. Lyophilized sterile alfafetoprotein administered intravenously in an amount of 2-10 mg in 12 ml of saline. After 2 min at About
the absence of adverse toxic effects
sterile substance doxorubicin-estrone in the number of 20 -
About 6 mg is dissolved in O, 5-1, 5 ml of 96% ethanol at heated to 70-76 0 with. The resulting solution was transferred to a 10 - 15 ml pre-warmed Lipidol ultrafluid.
30 The resulting suspension was cooled to z7Ds and injected under rentgenotelevideniya control into the hepatic artery.
After 3-4 weeks of conducting reintroduction aLfafetoproteina and substance doxorubicin-estrone as described above procedure. The ratio of alpha-fetoprotein and

35 agents doxorubicin-Lipiodol solution of estrone in ultrafluid in the body for the occasional injection of the drug is / mg / 10.2: 20-60, respectively.

Promymlennaya applicability

The proposed treatment for primary liver cancer and method of treatment with this medication have been used in clinics in Russia and gave a positive 5 results.

CLAIMS

1 • A tool for the suppression of tumor cell growth primary liver cancer, which contains the active substance and carrier, which is used as Lipiodol 5 ultrafluid, characterized in that as active ingredient used doxorubicin estrone, and carrier further comprises freeze-dried preparation of human alpha-fetoprotein.

2. The tool of claim 1, characterized in that the use 10 solution of doxorubicin in 96% ethanol in an amount 20-60 mg in 10-15 ml Lipiodol ultrafluida and 2-10 mg alpha protein in human cells 12-15 saline.

3. The tool of claim 2, characterized in that the use solution of estrone in the doxorubicin-heated to 70-76 0 C 15 etilovok alcohol.

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4. For the treatment of primary liver cancer, represents a set of separately packed includes number drugs, wherein a sterile doxorubicin 20-60 kg, Lipiodol in ultrafluid hermetically that the set estrone in number 10-15 kg, alpha-fetoprotein in the amount of 1.10 u.

5. The tool of claim 4, characterized in that it contains Saks known for his saline solution consisting of 15 cells and

96% ethanol at 5 cl.

6. A method for treating primary liver cancer, including preparing a solution of the active substance in Lipiodol ultrafluide and the introduction of this solution hepatic artery, featuring a tech, that as active substance use 20-60 cells, doxorubicin 30 estrone and dissolve it in 96% ethanol, heated to 70-76 0 C, was added in the amount of Lipiodol ultrafluida 35 10-15 cells, for 10-30 minutes prior to the introduction of this solution injected into the hepatic artery in alpha-fetoprotein number of 2-10 mg in 12-15 ml of saline solution.
7. The method according to claim 6, characterized in that described in p.6 way to repeat the treatment after 3-4 weeks.